REMARKS

Claims 1-58 were pending in this application. Upon entry of this amendment, claims 1-15, 21-51, and 56-58 will be pending. The amendment accompanying these remarks cancels claims 16-20 and 52-55 without prejudice to their presentation in a continuation or divisional application and amends claim 58 to more specifically define the same. A version of this claim with markings to show where changes have been made appears in Appendix A at the end of this communication.

Rejections Under 35 U.S.C. §103

Claims 1-15, 21-33, 38-51, and 56-58 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Winn *et al.* (5,707,144) in combination with Sarraj *et al.* It is the Examiner's position that because Winn ('144) discloses the instant compounds as known endothelin antagonists and Sarraj evaluates the effects an endothelin antagonist on bone growth, the combination of these teachings renders the instant methods prima facia obvious absent evidence of unexpected results since other ET-A compounds would have a positive effect on bone resorption.

Applicants traverse the rejection and respectfully request withdrawal of the same.

While the Examiner is correct in their assertion that Winn discloses the instant compounds as endothelin antagonists, Applicants respectfully submit that the combination of Winn and Sarraj do not teach the subject matter of claims 1, 21, 38 (and claims dependent thereon), and 56-57.

Sarraj is directed to study of an ***intra***-bone process, namely equilibrium between bone formation and resorption, which equilibrium is believed to contribute to homeostasis of bone mass and suspected by Sarraj to be regulated, at lease in part, by IL-6 production which, in turn, may be regulated by endothelin. This is disclosed in the abstract of Sarraj which states:

"[I]n this study we examined the effects ET-1 and ET-3 have on IL-6 and M-CSF production by osteoblasts"

and on page 3, second paragraph, of Sarraj which states:

"[F]or this study we proposed that ET alters production of M-CSF and/or IL-6 by OB, thereby affecting bone resorption through changing the cytokine balance in the bone marrow and ultimately altering the number and/or function of OC in bone".

For a combination of references to render a claimed invention unpatentable under 35 U.S.C. 103(a), the combination of references must teach, disclose, or suggest the claimed modification to one of ordinary skill in the art at the time of the invention.

The combination of Winn and Sarraj merely teaches an experiment in which the effects of ET-1 and ET-3 on IL-6 and M-CSF production by osteoblasts is modulated by an endothelin receptor antagonist disclosed in the '144 patent.

There is no teaching or suggestion by Winn in combination with Sarraj that endothelin antagonists may be useful for inhibition of an ***inter***-bone processes such as the transfer of a primary cancer from the cite of disease to bone, the measurement of which process is discussed from page 49 to page 51, line 14 of the subject application, and the results of which measurement are shown in Figure 6 of the same.

Therefore, because the combination of Winn and Sarraj has no bearing on claim 1 (and claims 2-10 dependent thereon), claim 11 (and claims 12-15 dependent thereon), claim 21 (and claims 22-29 dependent thereon), claim 38 (and claims 39-47 dependent thereon), and claims 56-58, the rejection is improper and should be withdrawn.

Claims 16-20 and 52-55 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Winn *et al.* (5,707,144) in combination with Tasker *et al.* It is the Examiner's position that because Tasker *et al.* discloses that endothelin antagonists are known to be useful for the treatment of bone pain associated with bone cancer, it would be obvious to one skilled in the art to use the endothelin antagonists of Winn *et al.* for the use of Tasker *et al.* since the compounds are endothelin antagonists and that this combination renders the instant method prima facia obvious absent evidence of unexpected results.

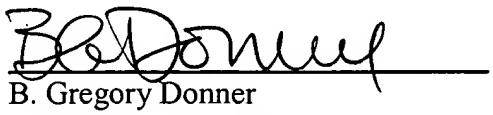
Applicants traverse the rejection and respectfully request withdrawal of the same.

In view of the cancellation of claims 16-20 and 52-55, the rejection is improper and should be withdrawn.

CONCLUSION

Allowance of claims 1-15, 21-51, and 56-58 is respectfully requested.

Respectfully submitted,
T. J. Janus, et al.



B. Gregory Donner
Registration No. 34,580
Agent for Applicants

23492

23492

ABBOTT LABORATORIES
Telephone: (847) 937-3810
Facsimile: (847) 938-2623

Appendix A

U.S. Application Ser. No. 09/923,616

VERSION OF CLAIMS WITH MARKINGS TO SHOW CHANGES MADE

58 (Amended). A method for inhibiting bone turnover in a patient **with bone metastases** which comprises administering to the patient in need thereof a therapeutically effective amount of an endothelin receptor antagonist.